REMARKS

I. Introductory Comments

Applicants request reconsideration of this application in view of the foregoing amendments and the following remarks.

Upon entry of the amendments, claims 13 and 31-35 will be pending in the application. Claims 1-12 and 14-30 currently are being cancelled. Claim 13 is being amended. Claims 31-35 are being added.

The following table shows where exemplary support for the claim amendments exists in the specification.

Claim	Exemplary Support
13	Pages 10-12 and 36-38
31-33	Page 94, lines 7-14
34	Paragraph bridging pages 51-52
35	Page 94, lines 23-26

In the specification, paragraphs have been amended on pages 1-2, 5-6, 76-77, 123, 127, 129-133, 170, 173-174, 185-186, 188, 190-191, 203-204 and 211. These amendments correct an obvious typographical error, remove internet addresses from the specification and substitute a new title of the invention. None of the amendments introduce new matter into the application.

II. Reconsideration of the Restriction Requirement

The Office made the restriction requirement final, but Applicants request reconsideration of that decision.

As noted in the response filed December 1, 2003, the 531-way restriction requirement runs counter to the PTO's own policy "to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office." MPEP 803.04. The Office has failed to articulate any rationale for suspending that policy, which permits examination of "up to ten (10) independent and distinct" sequences without restriction.

Additionally, unity of invention exists within the restricted Markush groups. According to MPEP 803.02, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. In this case, the claimed polynucleotides and polypeptides share substantial structural features indicative of their common utilities. All the polypeptides have defining protease structural features. At a more detailed level, proteins encoded by SEQ ID NOs: 60-62 share structural features indicative of Zn carboxypeptidase family of carboxypeptidase proteases; proteins encoded by SEQ ID NOs: 64-77 share structural features indicative of the UCH2b family of cysteine proteases; proteins encoded by SEQ ID NOs: 78-81 share structural features indicative of metalloproteases; and proteins encoded by SEQ ID NOs: 83-118 share structural features indicative of trypsin serine proteases.

For at least these reasons, Applicants maintain that the restriction requirement is improperly drawn.

III. Priority to U.S. Ser. No. 60/214,047

The Office acknowledged Applicants' claim for priority to U.S. Ser. No. 60/214,047 under 35 U.S.C. § 119(e), but denied that priority because "it would require undue effort on the part of the examiner to determine which, if any, of the sequences recited in the provisional application is identical to instant SEQ ID NOS." Applicants request reconsideration of that determination.

In denying priority, the Office bears an initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize a description of the claimed invention in the original disclosure. *See* MPEP § 2163 (II)(A)(3)(b); *In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976). In this case, however, the Office did not provide any evidence or reasoning as to why persons skilled in the art would not recognize a description of the claimed invention in the priority document. Instead, the Office simply determined that an evaluation of priority would require too much effort. The Office, therefore, has not satisfied the initial burden required to deny an application priority.

Moreover, the priority document, U.S. Ser. No. 60/214,047 actually contains significant support for the claimed invention. For instance, the priority document identifies as SGPr480 the protein represented by SEQ ID NO: 73 of the present application. The priority document provides a partial amino acid sequence (SEQ ID NO: 260) for the SGPr480 protein, and identifies the SGPr480 protein as being a cysteine protease of the UCH2b family (Figure 3A). In the paragraph bridging pages 63-64, the priority document describes "methods for identifying a substance that modulates [SGPr480] protease activity comprising the steps of: (a) contacting [SGPr480] with a test substance, (b) measuring the activity of said [SGPr480] polypeptide; and (c) determining whether said substance modulates the activity of said [SGPr480] polypeptide."

For at least these reasons, Applicants respectfully request that the Office grant this application priority to U.S. Ser. No. 60/214,047.

IV. Objections to the Specification

The Office objected to the specification for three reasons: (a) reference to a "nucleic acid molecule having amino acid sequence . . ." in the paragraph bridging pages 5-6, (b) reference to an "NRAA" database on pages 163-193, and (c) the presence of embedded hyperlinks on pages 123, 129 and 132.

Applicants have corrected the reference to a "nucleic acid molecule having amino acid sequence . . ." This was an obvious error, as each of the recited sequences was an amino acid sequence. The corrected passage now refers to a "polypeptide molecule having the amino acid sequence . . ." Because the error was obvious and the intended meaning was clear, the correction does not raise issues of new matter.

The Office stated that the meaning of the abbreviation "NRAA" is not clear, but that "[t]he issue is essential for identification of the identity of the claimed polypeptide." In response, Applicants direct the Examiner's attention to lines 13-14 on page 131 of the specification, which explains that "NRAA" stands for "NCBI non-redundant protein database." The NCBI non-redundant protein database is well-known and publicly accessible via the internet.

Finally, the Office objected to the specification for containing "an embedded hyperlink and/or other form of browser-executable code." In response to this objection, Applicants have removed all internet addresses from the specification.

For these reasons, Applicants request withdrawal of the objections to the specification.

V. Title and Abstract of the Invention

The Office alleged that the title and abstract of the invention are not descriptive, and required submission of a new title and abstract.

In compliance with that request, Applicants have amended the title and abstract by tailoring them to the invention of claim 13. Accordingly, Applicants request withdrawal of the objection.

VI. Claim 13 is Definite, in Accord with 35 U.S.C. § 112, Second Paragraph

Claim 13 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, the Office stated that it is not clear what relationship exists between monitoring cell features recited in step (c) and identification of a protease modulator. The Office also stated that the meaning of "substantially identical" is not clear because "no standard of reference has been provided with which to determine whether a particular sequence is 'substantially identical' or not." Applicants traverse these rejections.

A. Relationship between Monitoring Cell Functions and Identifying Modulators

In claim 13, the relationship between "identifying a substance that modulates the activity of a protease polypeptide in a cell" and "monitoring a change in cell phenotype, cell proliferation, cell differentiation or the interaction between said polypeptide and a natural binding partner" would be apparent to anyone of ordinary skill in the art. Pages 36-38 of the specification clearly indicate that after a cell expressing a protease is exposed to a test substance, changes in the recited cell features indicate that the test substance is a modulator of the protease. This relationship is implicit in claim 13.

To make the relationship *explicit* within claim 13, Applicants have amended the claim to recite that "a change in step (c) indicates that said test substance modulates the activity of said protease polypeptide." Because the amendment only makes *explicit* what previously was *implicit*, it does not change the scope of claim 13.

B. Meaning of "Substantially Identical"

Regarding the term "substantially identical," Applicants refer the Examiner to pages 10-12 of the specification, which equate "identity" with sequence "similarity" and define "substantially similar" sequences as those having at least 50%, 60%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity. Contrary to the Office's statement, this provides a clear "standard of reference" for determining if two sequences are substantially identical.

Nevertheless, the rejection is now moot, as amended claim 13 recites that the protease polypeptide comprises a sequence having at least 95% identity to that of SEQ ID NO: 73.

For at least these reasons, Applicants request withdrawal of the "indefiniteness" rejections.

VII. Claim 13 Meets the Utility and Enablement Requirements

Claim 13 was rejected under 35 U.S.C. §§ 101 and 112 because the claimed invention allegedly lacks a "specific and substantial asserted utility or a well established utility." In particular, the Office stated that the specification's assertion of utility is based on the results of a database search, but that (a) "it is not clear what kind of database was used," and (b) when "accession number NP-115971.1 . . . was searched in the NCBI database, it yielded a sequence of a protein which . . . does not have any sequence similarity with SEQ ID NO: 73." Additionally, the Office questioned the utility of polypeptides having sequences only "substantially identical" to that of SEQ ID NO: 73 because "limited homology . . . does not indicate what function [a polypeptide] might have." Applicants traverse this rejection.

First, as explained above, the specification clearly identifies the database used to identify homologous polypeptides. The last paragraph on page 170 states that a Smith Waterman search of the "NRAA" database identified accession number NP 115971.1. Lines

13-14 on page 131 explain that "NRAA" stands for "NCBI non-redundant protein database." The NCBI non-redundant protein database is well-known and publicly accessible via the internet.

Second, the amino acid sequence of accession number NP 115971.1 has 99.8% identity over the full length of SEQ ID NO: 73. As evidence of this high similarity, Applicants have attached the results of a BLAST comparison of the two sequences (Appendix I), showing 1272 matches across the 1274 residues of NP 115971.1. The striking similarity of SEQ ID NO: 73 to NP 115971.1, a ubiquitin specific protease of the UCH-2 family, clearly indicates that SEQ ID NO: 73 represents a protease of the same family.

Finally, while limited sequence similarity might have limited predictive value, the sequence similarity in this case is very high – exceeding 99%. The Examiner cited Skolnick *et al.*, Trends in Biotech., 18(1): 34-39 (2000) ("Skolnick") for the proposition that assigning functional activities for any particular polypeptide based on sequence homology can be inaccurate. Skolnick, however, acknowledges that the "sequence-to-function approach is the most commonly used function-prediction method" and that the field of predicting protein function from sequence data is "robust" and "well developed." Page 34, col. 2. Skolnick additionally acknowledges that methods of predicting protein function from sequence data are "powerful," despite certain limitations. *Id.*

Applicants submit that the predictive value of a sequence identity exceeding 99% meets the legal requirement for establishing the utility of an invention. It is not necessary to establish utility as a matter of statistical certainty or even beyond reasonable doubt. MPEP 2707.02(VII); *Nelson v. Bowler*, 626 F.2d 853 (CCPA 1980); *In re Irons*, 340 F.2d 974 (CCPA 1965). Rather, the supporting data must only be "reasonably predictive" and not contravene established scientific principles. MPEP 2707.02(VII); *Rey-Bellet v. Englehardt* 493 F.2d 1380 (CCPA 1974); *In re Gazave*, 379 F.2d 973 (CCPA 1967). The sequence identity in this case meets that requirement.

For at least these reasons, Applicants request withdrawal of the "utility" rejections.

VIII. Claim 13 Meets the Written Description Requirements

Claim 13 was rejected under 35 U.S.C. § 112, first paragraph, for an alleged lack of written description support. This rejection stemmed from the Office's concerns about the NRAA database and whether any sequence similarity actually exists between SEQ ID NO: 73 and the sequence of NP 115971.1. In light of those concerns, the Office stated that "there is no sufficient evidence of record demonstrating that the polypeptide comprising SEQ ID NO: 73 is a protease." Applicants traverse this rejection.

First, the facts do not raise a written description issue, as SEQ ID NO: 73 evidences possession of the polypeptide, and the specification explicitly states that SEQ ID NO: 73 represents a cysteine protease of the UCH2b family. See page 147, lines 20-26 and the paragraph bridging pages 170-171.

Also, as shown above, the NRAA database is clearly identified in the specification and SEQ ID NO: 73 has more than 99% sequence identity across the length of the NP 115971.1 sequence.

For at least these reasons, Applicants request withdrawal of the "written description" rejections.

IX. Concluding Remarks

The present application is in condition for allowance, and Applicants earnestly request favorable reconsideration of it.

If the Examiner believes that an interview would further advance prosecution, he is invited to contact the undersigned attorney by telephone.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of

papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 3 June 2004

By _____

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NCBI **Blast 2 Sequences results**

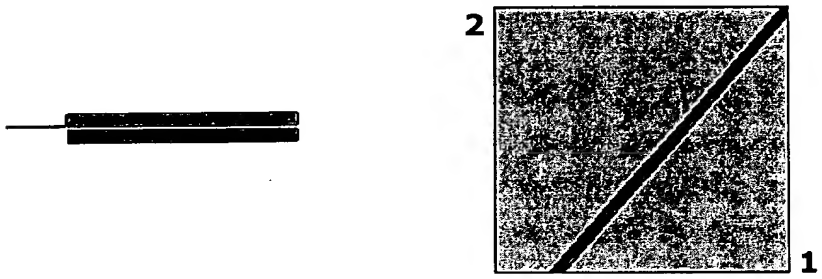
PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.6 [Apr-09-2003]

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 50 expect: 10.000 wordsize: 3 Filter ☐ Align

Sequence 1 lcl|seq_1 **Length** 1604 (1 .. 1604)

Sequence 2 gi 14211903 ubiquitin specific protease [Homo sapiens] **Length** 1274 (1 .. 1274)



NOTE:The statistics (bitscore and expect value) is calculated based on the size of nr database

Score = 2626 bits (6807), Expect = 0.0
Identities = 1272/1274 (99%), Positives = 1272/1274 (99%)

```
Query:   331  MGHLTLEDYQIWSVKNVLANEFLNLLFQVCHIVLGLRPATPEEEGQIIRGWL
              MGHLTLEDYQIWSVKNVLANEFLNLLFQVCHIVLGLRPATPEEEGQIIRGWL
Sbjct:   1    MGHLTLEDYQIWSVKNVLANEFLNLLFQVCHIVLGLRPATPEEEGQIIRGWL

Query:   391  QAGHNWFIISMQWWQQWKEYVKYDANPVVIEPSSVLNGGKYSFGTAAHPMEQ
              QAGHNWFIISMQWWQQWKEYVKYDANPVVIEPSSVLNGGKYSFGTAAHPMEQ
Sbjct:   61   QAGHNWFIISMQWWQQWKEYVKYDANPVVIEPSSVLNGGKYSFGTAAHPMEQ

Query:   451  LSYVNTTEEKFSDNISTASEASETAGSGFLYSATPGADVCFARQHNTSDNNN
              LSYVNTTEEKFSDNISTASEASETAGSGFLYSATPGADVCFARQHNTSDNNN
Sbjct:   121  LSYVNTTEEKFSDNISTASEASETAGSGFLYSATPGADVCFARQHNTSDNNN

Query:   511  NILLHLNPQKPGAIDNQPLVTQEPVKATSLTLEGGRLKRTPQLIHGRDYEMV
              NILLHLNPQKPGAIDNQPLVTQEPVKATSLTLEGGRLKRTPQLIHGRDYEMV
Sbjct:   181  NILLHLNPQKPGAIDNQPLVTQEPVKATSLTLEGGRLKRTPQLIHGRDYEMV

Query:   571  YHWYGANLALPRPVIKNSKTDIPELELFPRYLLFLRQQPATRTQQSNIWVNM
              YHWYGANLALPRPVIKNSKTDIPELELFPRYLLFLRQQPATRTQQSNIWVNM
Sbjct:   241  YHWYGANLALPRPVIKNSKTDIPELELFPRYLLFLRQQPATRTQQSNIWVNM

Query:   631  PLKRVLAYTGCFSRMQTIKEIHEYLSQRLRIKEEDMRLWLYNSENYLTLLDD
              PLKRVLAYTGCFSRMQTIKEIHEYLSQRLRIKEEDMRLWLYNSENYLTLLDD
Sbjct:   301  PLKRVLAYTGCFSRMQTIKEIHEYLSQRLRIKEEDMRLWLYNSENYLTLLDD

Query:   691  KIQDEQHLVIEVRNKDMSWPEEMSFIANSSKIDRHKVPTEKGATGLSNLGNT
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                                     KIQDEQHLVIEVRNKDMSWPEEMSFIANSSKIDRHKVPTEKGATGLSNLGNT
Sbjct:                          361  KIQDEQHLVIEVRNKDMSWPEEMSFIANSSKIDRHKVPTEKGATGLSNLGNT
Ubiquitin carboxyl-terminal hyd> 404                                          *********

Query:                          751  CVSNTQPLTQYFISGRHLYELNRTNPIGMKGHMAKCYGDLVQELWSGTQKNV
                                     CVSNTQPLTQYFISGRHLYELNRTNPIGMKGHMAKCYGDLVQELWSGTQKNV
Sbjct:                          421  CVSNTQPLTQYFISGRHLYELNRTNPIGMKGHMAKCYGDLVQELWSGTQKNV
Ubiquitin carboxyl-terminal hyd> 421  **************

Query:                          811  IAKYAPRFNGFQQQDSQELLAFLLDGLHEDLNRVHEKPYVELKDSDGRPDWE
                                     IAKYAPRFNGFQQQDSQELLAFLLDGLHEDLNRVHEKPYVELKDSDGRPDWE
Sbjct:                          481  IAKYAPRFNGFQQQDSQELLAFLLDGLHEDLNRVHEKPYVELKDSDGRPDWE

Query:                          871  HLRRNRSIVVDLFHGQLRSQVKCKTCGHISVRFDPFNFLSLPLPMDSYMHLE
                                     HLRRNRSIVVDLF GQLRSQVKCKTCGHISVRFDPFNFLSLPLPMDSYMHLE
Sbjct:                          541  HLRRNRSIVVDLFRGQLRSQVKCKTCGHISVRFDPFNFLSLPLPMDSYMHLE

Query:                          931  TTPVRYGLRLNMDEKYTGLKKQLSDLCGLNSEQILLAEVHGSNIKNFPQDNQ
                                     TTPVRYGLRLNMDEKYTGLKKQLSDLCGLNSEQILLAEVHGSNIKNFPQDNQ
Sbjct:                          601  TTPVRYGLRLNMDEKYTGLKKQLSDLCGLNSEQILLAEVHGSNIKNFPQDNQ

Query:                          991  FLCAFEIPVPVSPISASSPTQTDFSSSPSTNEMFTLTTNGDLPRPIFIPNGM
                                     FLCAFEIPVPVSPISASSPTQTDFSSSPSTNEMFTLTTNGDLPRPIFIPNGM
Sbjct:                          661  FLCAFEIPVPVSPISASSPTQTDFSSSPSTNEMFTLTTNGDLPRPIFIPNGM

Query:                          1051 TEKNFTNGMVNGHMPSLPDSPFTGYIIAVHRKMMRTELYFLSSQKNRPSLFG
                                     TEKNFTNGMVNGHMPSLPDSPFTGYIIAVHRKMMRTELYFLSSQKNRPSLFG
Sbjct:                          721  TEKNFTNGMVNGHMPSLPDSPFTGYIIAVHRKMMRTELYFLSSQKNRPSLFG

Query:                          1111 VHTRKKDLYDAVWIQVSRLASPLPPQEASNHAQDCDDSMGYQYPFTLRVVQK
                                     VHTRKKDLYDAVWIQVSRLASPLPPQEASNHAQDCDDSMGYQYPFTLRVVQK
Sbjct:                          781  VHTRKKDLYDAVWIQVSRLASPLPPQEASNHAQDCDDSMGYQYPFTLRVVQK

Query:                          1171 PWYRFCRGCKIDCGEDRAFIGNAYIAVDWDPTALHLRYQTSQERVVDEHESV
                                     PWYRFCRGCKIDCGEDRAFIGNAYIAVDWDPTALHLRYQTSQERVVDEHESV
Sbjct:                          841  PWYRFCRGCKIDCGEDRAFIGNAYIAVDWDPTALHLRYQTSQERVVDEHESV

Query:                          1231 EPINLDSCLRAFTSEEELGENEMYYCSKCKTHCLATKKLDLWRLPPILIIHL
                                     EPINLDSCLRAFTSEEELGENEMYYCSKCKTHCLATKKLDLWRLPPILIIHL
Sbjct:                          901  EPINLDSCLRAFTSEEELGENEMYYCSKCKTHCLATKKLDLWRLPPILIIHL

Query:                          1291 RWIKSQKIVKFPRESFDPSAFLVPRDPALCQHKPLTPQGDELSEPRILAREV
                                     RWIKSQKIVKFPRESFDPSAFLVPRDPALCQHKPLTPQGDELSEPRILAREV
Sbjct:                          961  RWIKSQKIVKFPRESFDPSAFLVPRDPALCQHKPLTPQGDELSEPRILAREV

Query:                          1351 AGEEDVLLSKSPSSLSANIISSPKGSPSSSRKSGTSCPSSKNSSPNSSPRTL
                                     AGEEDVLLSKSPSSLSANIISSPKGSPSSSRKSGTSCPSSKNSSPNSSPRTL
Sbjct:                          1021 AGEEDVLLSKSPSSLSANIISSPKGSPSSSRKSGTSCPSSKNSSPNSSPRTL

Query:                          1411 LPQIGSKNKLSSSKENLDASKENGAGQICELADALSRGHVLGGSQPELVTPQ
                                     LPQIGSKNKLSSSKENLDASKENGAGQICELADALSRGHVLGGSQPELVTPQ
Sbjct:                          1081 LPQIGSKNKLSSSKENLDASKENGAGQICELADALSRGHVLGGSQPELVTPQ

Query:                          1471 GFLYEHEACGNGYSNGQLGNHSEEDSTDDQREDTRIKPIYNLYAISCHSGIL
                                     GFLYEHEACGNGYSNGQLGNHSEEDSTDDQREDTRIKPIYNLYAISCHSGIL
Sbjct:                          1141 GFLYEHEACGNGYSNGQLGNHSEEDSTDDQREDTRIKPIYNLYAISCHSGIL
Ubiquitin carboxyl-terminal hyd> 1179                                         **************

Query:                          1531 AKNPNCKWYCYNDSSCKELHPDEIDTDSAYILFYEQQGIDYAQFLPKTDGKK
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Sbjct:                          1201 AKNPNCKWYCYNDSSCKELHPDEIDTDSAYILFYEQQGIDYAQFLPKTDGKK
Ubiquitin carboxyl-terminal hyd> 1201 ************************************
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Query:                          1591 EDFESDYKKYCVLQ 1604
                                     EDFESDYKKYCVLQ
Sbjct:                          1261 EDFESDYKKYCVLQ 1274

CPU time:      0.12 user secs.       0.02 sys. secs          0.14 total secs.

Lambda      K       H
   0.317    0.134    0.410

Gapped
Lambda      K       H
   0.267   0.0410    0.140


Matrix: BLOSUM62
Gap Penalties: Existence: 11, Extension: 1
Number of Hits to DB: 20,645
Number of Sequences: 0
Number of extensions: 1536
Number of successful extensions: 4
Number of sequences better than 10.0: 1
Number of HSP's better than 10.0 without gapping: 1
Number of HSP's successfully gapped in prelim test: 0
Number of HSP's that attempted gapping in prelim test: 0
Number of HSP's gapped (non-prelim): 2
length of query: 1274
length of database: 759,694,065
effective HSP length: 143
effective length of query: 1131
effective length of database: 759,693,922
effective search space: 859213825782
effective search space used: 859213825782
T: 9
A: 40
X1: 16 ( 7.3 bits)
X2: 129 (49.7 bits)
X3: 129 (49.7 bits)
S1: 41 (21.6 bits)
S2: 83 (36.6 bits)
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